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Published in:
Jacc-Cardiovascular interventions

DOI:
10.1016/j.jcin.2015.11.036

JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 9, NO. 5, 2016

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcin.2015.11.036

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Long-Term Outcome of Alcohol Septal Ablation for Obstructive Hypertrophic Cardiomyopathy in the Young and the Elderly

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ABSTRACT

OBJECTIVES The aim of this study was to compare outcomes of alcohol septal ablation (ASA) in young and elderly patients with obstructive hypertrophic cardiomyopathy (HCM).

BACKGROUND The American College of Cardiology Foundation/American Heart Association guidelines reserve ASA for elderly patients and patients with serious comorbidities. Information on long-term age-specific outcomes after ASA is scarce.

METHODS This cohort study included 217 HCM patients (age 54 ± 12 years) who underwent ASA because of symptomatic left ventricular outflow tract obstruction. Patients were divided into young (age ≤55 years) and elderly (age >55 years) groups and matched by age in a 1:1 fashion to nonobstructive HCM patients.

RESULTS Atrioventricular block following ASA was more common in elderly patients (43% vs. 21%; p = 0.001), resulting in pacemaker implantation in 13% and 5%, respectively (p = 0.06). Residual left ventricular outflow tract gradient, post-procedural New York Heart Association functional class, and necessity for additional septal reduction therapy was comparable between age groups. During a follow-up of 7.6 ± 4.6 years, 54 patients died. The 5- and 10-year survival following ASA was 95% and 90% in patients age ≤55 years and 93% and 82% in patients age >55 years, which was comparable to their control groups. The annual adverse arrhythmic event rate following ASA was 0.7%/year in young patients and 1.4%/year in elderly patients, which was comparable to their control groups.

CONCLUSIONS ASA is similarly effective for reduction of symptoms in young and elderly patients; however, younger patients have a lower risk of procedure-related atrioventricular conduction disturbances. The long-term mortality rate and risk of adverse arrhythmic events following ASA are low, both in young and elderly patients, and are comparable to age-matched nonobstructive HCM patients. (J Am Coll Cardiol Intv 2016;9:463–9) © 2016 by the American College of Cardiology Foundation.

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Manuscript received August 16, 2015; revised manuscript received November 2, 2015, accepted November 19, 2015.

ABBREVIATIONS AND ACRONYMS

AAE = adverse arrhythmic event(s)

ASA = alcohol septal ablation

CI = confidence interval

HCM = hypertrophic cardiomyopathy

ICD = implantable cardioverter-defibrillator

LVOT = left ventricular outflow tract

LVWT = left ventricular wall thickness

NYHA = New York Heart Association

SCD = sudden cardiac death

If patients with obstructive hypertrophic cardiomyopathy (HCM) remain severely symptomatic despite optimal medical therapy, septal reduction therapy should be considered. This can be done either by surgical myectomy or alcohol septal ablation (ASA) (1,2). ASA was introduced as a percutaneous alternative to surgical myectomy and has been shown to be effective in reducing left ventricular outflow tract (LVOT) obstruction and associated symptoms in the 20 years since (3–5). Concerns about ASA remain, however, especially about the possible arrhythmogenic effect of the ablation scar in patients who are already at an increased risk of life-threatening arrhythmias (6). The American College of Cardiology Foundation/American Heart Association guidelines on HCM state that ASA should be reserved for elderly patients and patients with serious comorbidities (1). Little is known about the differences in outcome of the procedure between young and elderly patients. The aim of this study was to compare complication rates, symptom relief, and long-term outcomes of ASA in young and elderly patients.

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METHODS

STUDY DESIGN AND PATIENT POPULATION. A multicenter observational cohort design was used. The study population consisted of 217 consecutive HCM patients who underwent ASA in the St. Antonius Hospital Nieuwegein, Nieuwegein, the Netherlands (n = 147), or the Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands (n = 70). All patients met the criteria for invasive treatment: 1) ventricular septal thickness ≥15 mm; 2) (provocable) LVOT gradient ≥50 mm Hg; and 3) persistent New York Heart Association (NYHA) functional class III/IV dyspnea or Canadian Cardiovascular Society class III/IV angina despite optimal medical therapy (1,2). The choice of ASA instead of surgical myectomy was made on the basis of patient profile (age, comorbidities, and so on) and patient preference. ASA was performed as described previously (7,8). All patients gave informed consent prior to the procedure. Local institutional review board approval was obtained. Patients were divided into groups by age: ≤55 and >55 years. The cutoff of 55 years was chosen because this was the median age of the study population (range 18 to 80 years). For the long-term outcomes, 2 control groups were selected from a cohort of 349 nonobstructive HCM patients, also used as the control group in a previous analysis (9). These patients, from the St. Antonius Hospital Nieuwegein, Erasmus Medical Center Rotterdam, and University Hospital Leuven (Belgium), all had an LVOT gradient of <30 mm Hg after provocation. Control subjects were matched by age to within 1 year of patients who underwent ASA.

FOLLOW-UP AND ENDPOINTS. Follow-up started at the time of ASA or, for the nonobstructive patients, at first outpatient clinic contact after January 1, 1990. At baseline, all patients were evaluated for the following characteristics: age, sex, NYHA functional class, maximum left ventricular wall thickness (LVWT), maximum (provocable) LVOT gradient, left ventricular function, coronary artery disease, atrial fibrillation, and conventional risk factors for sudden cardiac death (SCD) (1).

The primary endpoints of this study were all-cause mortality and adverse arrhythmic events (AAEs) during long-term follow-up (i.e., after 30 days post-procedure). AAEs consisted of SCD, resuscitated cardiac arrest due to ventricular fibrillation or tachycardia, and appropriate implantable cardioverter-defibrillator (ICD) shock. Secondary endpoints were HCM-related death (death due to heart failure, stroke, or SCD); periprocedural (<30 days) mortality and AAEs; new right bundle branch block; (temporary) atrioventricular block; permanent pacemaker implantation; ICD implantation; reduction in LVWT, LVOT gradient, and NYHA functional class >3 months post-procedure; and reintervention (ASA or myectomy).

Mortality and adverse events were retrieved from hospital patient records at the center where follow-up occurred, from civil service population registers, and from information provided by patients themselves and/or their general practitioners. All ICD shocks were evaluated by an experienced electrophysiologist who was unaware and independent of the study purpose and endpoints. If no events occurred during follow-up, the administrative censoring date was set at November 1, 2012.

STATISTICAL ANALYSIS. SPSS version 20.0 (IBM, Armonk, New York) and Microsoft Excel 2010 (Microsoft Corporation, Redmond, Washington) were used for all statistical analyses. Categorical variables were summarized as percentages. Normally distributed continuous data are expressed as mean ± SD, and non-normally distributed data are expressed as median (interquartile range). To compare continuous variables, the Student *t* test or Mann-Whitney *U* test were used, and to compare categorical variables, the chi-square test was used. Because age does not allow

TABLE 1 Baseline Characteristics of 107 Patients Age ≤55 Years and 110 Patients Age >55 Years Undergoing ASA and Their Age-Matched Control Groups

	ASA ≤55 yrs (n = 107)	Control ≤55 yrs (n = 107)	p Value	ASA >55 yrs (n = 110)	Control >55 yrs (n = 110)	p Value	Comparison p Value
Age, yrs	43 ± 8	43 ± 8	0.99	64 ± 6	64 ± 6	0.98	<0.001
Female	21 (20%)	30 (28%)	0.20	54 (49%)	39 (36%)	0.056	<0.001
NYHA functional class III/IV	90 (84%)	9 (8%)	<0.001	84 (76%)	18 (16%)	<0.001	0.21
Maximum LVWT, mm	20 ± 6	18 ± 5	<0.001	19 ± 4	18 ± 5	0.17	0.001
Maximum LVOT gradient, mm Hg	65 ± 56	6 ± 5	<0.001	60 ± 63	7 ± 5	<0.001	0.68
Systolic dysfunction (EF <50%)	2 (2%)	15 (14%)	0.002	10 (9%)	25 (23%)	0.010	0.042
Coronary artery disease	8 (8%)	12 (11%)	0.48	37 (34%)	18 (16%)	0.005	<0.001
Atrial fibrillation	20 (19%)	29 (27%)	0.19	26 (24%)	47 (43%)	0.004	0.47
Sudden cardiac death survivor	4 (4%)	8 (8%)	0.38	2 (2%)	11 (10%)	0.022	0.44
≥2 conventional risk factors for SCD	16 (15%)	16 (15%)	1.0	9 (8%)	22 (20%)	0.020	0.18
Amount of alcohol, ml	3.0 (1.0)	–	–	2.0 (1.0)	–	–	0.013

Values are n (%), mean ± SD, or median (interquartile range).

ASA = alcohol septal ablation; EF = ejection fraction; LVOT = left ventricular outflow tract; LVWT = left ventricular wall thickness; NYHA = New York Heart Association; SCD = sudden cardiac death.

for exact matching, analyses were performed on independent groups. Kaplan-Meier graphs were used to show survival rates. In all analyses, a p value <0.05 was considered significant.

RESULTS

CLINICAL CHARACTERISTICS. The baseline characteristics of the 217 patients who underwent ASA and their age-matched control subjects are shown in Table 1. The mean age of the patients ≤55 years was 43 ± 8 years, and the mean age of the patients >55 years was 64 ± 6 years. There were more nonobstructive patients with systolic dysfunction compared with patients who underwent ASA. A higher alcohol dose was used for ASA in patients age ≤55 years compared with patients age >55 years (p = 0.013).

PROCEDURAL OUTCOMES. Procedural outcomes of the patients who underwent ASA are shown in Table 2. Atrioventricular block following ASA was more common in patients age >55 years compared with patients age ≤55 years (43% vs. 21%; p = 0.001), resulting in permanent pacemaker implantation in 13% and 5%, respectively (p = 0.06). Other periprocedural complications, including AAEs and mortality, were similar in both groups. Residual LVWT, LVOT gradient, and NYHA functional class >3 months post-procedure were comparable in both age groups, as was the necessity for additional septal reduction therapy.

LONG-TERM OUTCOMES. During a mean follow-up of 7.6 ± 4.6 years, there were a total of 20 deaths in the ASA cohorts and 34 deaths in the control groups (Tables 3 and 4). Follow-up was complete in 98% of patients. The 5- and 10-year survival following ASA of patients age ≤55 years was 94.9% (95% confidence interval [CI]: 90.4% to 100.0%) and 90.2% (95% CI: 82.2% to 98.1%), respectively, compared with 98.0% (95% CI: 95.4% to 100.0%) and 88.1% (95% CI: 80.1% to 96.1%) in the control group (p = 0.87) (Figure 1). The 5- and 10-year survival following ASA of patients age >55 years was 93.2% (95% CI: 88.0% to 98.5%) and 81.9% (95% CI: 71.8% to 91.9%), respectively, compared with 91.7% (95% CI: 86.1% to 97.3%) and 82.7% (95% CI: 72.9% to 92.6%) in the control group (p = 0.51) (Figure 2). The annual AAE rate following ASA in patients age ≤55 years was 0.7%/year compared with 1%/year in the control group (p = 0.6).

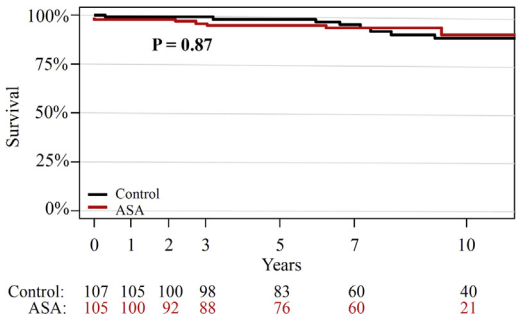
TABLE 2 Procedural Outcomes After Alcohol Septal Ablation in 107 Patients Age ≤55 Years and 110 Patients Age >55 Years

	ASA ≤55 yrs (n = 107)	ASA >55 yrs (n = 110)	p Value
Periprocedural (<30 days) complications			
New right bundle branch block	42 (39%)	39 (36%)	0.66
(Temporary) atrioventricular block	22 (21%)	47 (43%)	0.001
Permanent pacemaker implantation	5 (5%)	14 (13%)	0.063
ICD implantation	15 (14%)	11 (10%)	0.48
Adverse arrhythmic events	8 (8%)	8 (7%)	1.0
Mortality	2 (2%)	0 (0%)	0.24
Procedure efficacy			
Residual LVWT >3 months post-procedure, mm	14 ± 5	14 ± 4	0.45
Residual LVOT gradient >3 months post-procedure, mm Hg	12 ± 27	10 ± 27	0.99
Reduction in LVOT gradient >3 months post-procedure, %	78 ± 60	76 ± 60	0.68
NYHA functional class III/IV >3 months post-procedure	5 (5%)	9 (9%)	0.43
Redo septal reduction therapy	14 (13%)	13 (12%)	0.94

Values are n (%) or mean ± SD.

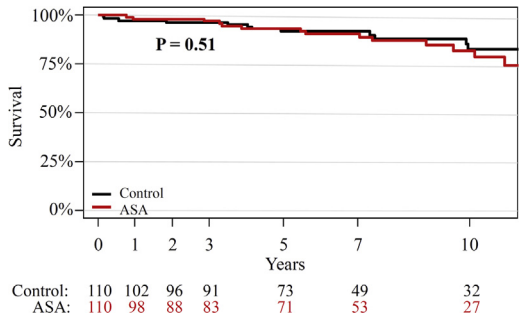
ICD = internal cardioverter defibrillator; other abbreviations as in Table 1.

FIGURE 1 Kaplan-Meier Graph of All-Cause Survival in Patients Age ≤55 Years Who Underwent ASA Versus Age-Matched Nonobstructive HCM Patients



ASA = alcohol septal ablation; HCM = hypertrophic cardiomyopathy.

FIGURE 2 Kaplan-Meier Graph of All-Cause Survival in Patients Age >55 Years Who Underwent ASA Versus Age-Matched Nonobstructive HCM patients



Abbreviations as in Figure 1.

The annual AAE rate following ASA in patients age >55 years was 1.4%/year compared with 0.5%/year in the control group (p = 0.07).

DISCUSSION

The most important result of this 7.6-year follow-up study is that long-term survival following ASA in young and elderly patients is comparable to survival in age-matched nonobstructive HCM patients, and the same holds true for AAE rates. Furthermore, ASA is similarly effective for reduction of symptoms in young and elderly patients, although younger patients have a lower risk of procedure-related atrioventricular conduction disturbances.

PREVIOUS AGE-SPECIFIC ASA STUDIES. Currently, information on the long-term age-specific outcomes after ASA in patients with obstructive HCM is scarce. Two previous studies (10,11) have evaluated age-specific outcomes of ASA patients during a follow-up period of 1 and 5.1 years, respectively. Leonardi et al. (10) compared the outcomes of 360 HCM patients undergoing ASA in 3 age categories (<45, 45 to 64, and >65 years). Likewise, they found that the reductions in LVOT gradient and NYHA functional class following ASA were similar independent of age and that elderly patients more often required pacemaker implantation after the procedure. There were no control groups, however, and not surprisingly, the mortality rate after a follow-up of 1 year was highest in patients age >65 years. Veselka et al. (11) assessed the 5.1-year outcomes following ASA in 75 patients age 42 ± 7 years, which is comparable to the mean age of our young patients. They found a survival free of all-cause mortality at 5 and 10 years of 94% each, which is in line with our findings. No comparisons with elderly patients were made, however.

CURRENT GUIDELINES. The American College of Cardiology Foundation/American Heart Association guidelines on HCM of 2011 state that ASA should be reserved for elderly patients and patients with serious comorbidities, and gives a Class III recommendation (Level of Evidence: C) to ASA for younger patients if myectomy is a viable option (1). The procedural mortality rate is reported to be <1% for myectomy versus up to 4% for ASA (1,12–14). Larger, more recent ASA studies have shown rates of 0.3% to 0.6%, however (15,16). Also, a recent meta-analysis comparing ASA to myectomy showed similarly low periprocedural and long-term mortality rates (17). Furthermore, subsequent to the publication of the 2011 guidelines, the post-ASA prognosis was demonstrated to be comparable with the sex- and age-matched population (15,16,18) and with matched post-myectomy patients (18). Notably, these and other studies (15,16,19) showed that age was the only independent predictor of mortality following ASA, implying that survival in patients after ASA is not determined by ASA, but by HCM itself.

One of the main concerns about ASA in younger patients is the potential arrhythmogenic effect of the ablation scar in patients who are already at an increased risk of life-threatening arrhythmias (6). Recent studies have shown, however, that the long-term risk of SCD after ASA is low and comparable to patients who undergo myectomy (9,17,18). This study showed an annual AAE rate following ASA of 0.7%/year in the young patients, which was similar to age-matched nonobstructive HCM patients and one-half the rate of elderly patients.

TABLE 3 Long-Term Outcomes After Alcohol Septal Ablation in 107 Patients Age ≤55 Years Compared With Their Age-Matched Control Group

	ASA ≤55 yrs (n = 107)	Control ≤55 yrs (n = 107)	p Value
Follow-up, yrs	7.2 ± 3.4	9.2 ± 5.6	
Mortality (>30 days post-procedure)			
Total mortality	5 (5%)	15 (14%)	0.036
HCM-related death	3 (3%)	11 (10%)	0.055
Noncardiac	2 (2%)	4 (4%)	0.68
5-yr survival, %	95	98	0.87
10-yr survival, %	90	88	0.87
Adverse arrhythmic events (>30 days post-procedure)			
Total adverse events	5 (5%)	9 (8%)	0.41
Sudden cardiac death	2 (2%)	4 (4%)	0.68
Resuscitated cardiac arrest	1 (1%)	2 (2%)	1.0
Appropriate ICD shocks	2 (2%)	3 (3%)	1.0
Annual events, %/yr	0.7	1.0	0.58

Values are mean ± SD or n (%). ASA = alcohol septal ablation; HCM = hypertrophic cardiomyopathy; ICD = internal cardioverter defibrillator.

TABLE 4 Long-Term Outcomes After Alcohol Septal Ablation in 107 Patients Age >55 Years Compared With Their Control Group

	ASA >55 yrs (n = 110)	Control >55 yrs (n = 110)	p Value
Follow-up, yrs	6.5 ± 3.8	7.5 ± 4.8	
Mortality (>30 days post-procedure)			
Total mortality	15 (14%)	19 (17%)	0.58
HCM-related death	4 (4%)	10 (9%)	0.17
Noncardiac	11 (10%)	8 (7%)	0.63
5-yr survival, %	93	92	0.51
10-yr survival, %	82	83	0.51
Adverse arrhythmic events (>30 days post-procedure)			
Total adverse events	10 (9%)	4 (4%)	0.17
Sudden cardiac death	3 (3%)	0 (0%)	0.25
Resuscitated cardiac arrest	2 (2%)	1 (1%)	1.0
Appropriate ICD shocks	5 (5%)	3 (3%)	0.72
Annual events, %/yr	1.4	0.5	0.070

Values are mean ± SD or n (%). Abbreviations as in Table 3.

Another conceivable reason to choose myectomy instead of ASA in younger patients is the >2× higher risk of atrioventricular block requiring pacemaker implantation following ASA (17,20). This higher need for pacemaker implantation may at least partly be explained by the higher age of the patients undergoing ASA: the ASA patients from both meta-analyses were on average 9 years older than the myectomy patients. The present and previous studies have shown that atrioventricular conduction disturbances following ASA are mainly seen in elderly patients (10,21), with a need for pacemaker implantation in only 5% of the young patients, despite a higher amount of alcohol use in the young patients. Large outcome studies following myectomy in HCM patients of similar age categories (mean age 37 to 47 years) showed incidences of atrioventricular block requiring pacemaker implantation of 1% to 6% (12,13,22,23).

Because the improvement in functional status following ASA in young and elderly patients is similarly good, we propose that the indication for ASA can be broadened to younger patients. In other words, younger age alone should not be a reason to exclude ASA. For children and adolescents, however, little to no results are available following ASA, although there is substantial experience with myectomy (24). We therefore recommend against ASA in this age group until studies have proven the safety and efficacy of the procedure in these very young patients.

PATIENT SELECTION AND SPECIALIZED CARE. In line with the 2011 American College of Cardiology (1) and the 2014 European Society of Cardiology (2) guidelines, we recommend that all patients considered for septal reduction therapy are assessed by a multidisciplinary heart team (consisting of at least 1 cardiothoracic surgeon, an interventional cardiologist, and a cardiologist specialized in the care of patients with HCM) to determine the optimal therapy by taking into account not only age, but also factors such as mitral valve anatomy, coronary anatomy, septal thickness, and comorbidities. When both procedures are possible, shared decision making between the informed patient and treating physician should also be part of the equation. Furthermore, septal reduction therapy should be performed by experienced operators and confined to centers with substantial and specific expertise in HCM care.

STUDY LIMITATIONS. There were significant differences in baseline characteristics between the young and elderly patients who underwent ASA. Besides the expected differences in prevalence of systolic dysfunction and coronary artery disease, we noted higher amounts of alcohol use in the age ≤55 years population. The same also held true in a recent study comparing the use of low (≤2 ml) versus high (>2 ml) doses of alcohol for ASA (25). In this study of the same patient population as the present study, patients from the high-dose group were significantly younger than those from the low-dose group. Although the 2 groups did not differ in maximal LVWT or LVOT gradient, the patients from the high-dose group did have larger target septal perforator(s), which might explain the difference.

This study has several other limitations. The study was performed in tertiary referral centers for

the care of HCM, and the patient population might not represent the general HCM population. This referral and selection bias could have influenced the results. Data collection was limited to variables that were routinely collected. We did not correct for individual or local alterations of percutaneous technique. However, all procedures were performed by experienced interventional cardiologists, and this implies that our findings are more generalizable than those of single-center investigations.

CONCLUSIONS

ASA is similarly effective for reduction of symptoms in young and elderly patients; however, younger patients have a lower risk of procedure-related atrioventricular conduction disturbances. The long-term mortality rate and risk of AAEs following ASA is low, both in young and elderly patients, and is comparable to age-matched nonobstructive HCM patients. We propose that the indication for ASA can be broadened to younger patients.

ACKNOWLEDGMENT The authors thank J.C. Kelder, MD, PhD, Department of Cardiology, St. Antonius Hospital Nieuwegein, for his statistical assistance.

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PERSPECTIVES

WHAT IS KNOWN? The American College of Cardiology Foundation/American Heart Association guidelines reserve ASA for elderly patients and patients with serious comorbidities. Information on long-term age-specific outcomes after ASA is scarce.

WHAT IS NEW? We found that ASA is similarly effective for reduction of symptoms in young and elderly patients and that the long-term mortality rate and risk of AAEs following ASA in young and elderly patients is comparable to age-matched nonobstructive HCM patients.

WHAT IS NEXT? We propose that the indication for ASA can be broadened to younger patients. However, more studies with long-term follow-up of young HCM patients undergoing ASA are warranted to confirm these findings.

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KEY WORDS alcohol septal ablation, hypertrophic cardiomyopathy, septal reduction therapy